National Library of Medicine: IGM Results Screen

Citations 1 to 9 of 9 from MEDLINE

☐ **TITLE:** CD40 antibodies defining distinct epitopes display qualitative differences in their induction of B-cell differentiation.
Full Citation **AUTHORS:** Bjorck P, Paulie S
SOURCE: Immunology. 1996 Feb;87(2):291-5.
Related Articles **CIT. IDS:** PMID: 8698393 UI: 96245984

☐ **TITLE:** Antibodies to distinct epitopes on the CD40 molecule co-operate in stimulation and can be used for the detection of soluble CD40.
Full Citation **AUTHORS:** Bjorck P, Braesch-Andersen S, Paulie S
SOURCE: Immunology. 1994 Nov;83(3):430-7.
Related Articles **CIT. IDS:** PMID: 7530692 UI: 95137673

☐ **TITLE:** CD40 plays an essential role in the activation of human B cells by murine EL4B5 cells.
Full Citation **AUTHORS:** Kwekkeboom J, De Boer M, Tager JM, De Groot C
SOURCE: Immunology. 1993 Jul;79(3):439-44.
Related Articles **CIT. IDS:** PMID: 7691726 UI: 94011036

☐ **TITLE:** Agonistic properties of anti-B cell antibodies purified on staphylococcal protein A may be due to contaminating protein A.
Full Citation **AUTHORS:** Jakobson E, Axelsson B, Paulie S
SOURCE: J Immunol Methods. 1992 Jul 31;152(1):49-57.
Related Articles **CIT. IDS:** PMID: 1379276 UI: 92348908

☐ **TITLE:** The human B lymphocyte and carcinoma antigen, CDw40, is a phosphoprotein involved in growth signal transduction.

Full Citation

AUTHORS: Paulie S, Rosen A, Ehlin-Henriksson B, Braesch-Andersen S, Jakobson E, Koho H, Perlmann P

SOURCE: J Immunol. 1989 Jan 15;142(2):590-5.

Related Articles CIT. IDS: PMID: 2463310 UI: 89093945

☐ TITLE: Isolation and characterization of two bladder carcinoma-associated antigens.

Full Citation AUTHORS: Braesch-Andersen S, Paulie S, Koho H, Perlmann P

SOURCE: J Immunol Methods. 1986 Nov 20;94(1-2):145-51.

Related Articles CIT. IDS: PMID: 3782807 UI: 87059074

☐ TITLE: Monoclonal antibodies against human urinary bladder carcinomas: selectivity and utilization for gamma scintigraphy.

Full Citation AUTHORS: Bubenik J, Kieler J, Perlmann P, Paulie S, Koho H, Christensen B, Dienstbier Z, Koprivova H, Pospisil J, Pouckova P, et al.

SOURCE: Eur J Cancer Clin Oncol. 1985 Jun;21(6):701-10.

Related Articles CIT. IDS: PMID: 3894033 UI: 85257727

☐ TITLE: A p50 surface antigen restricted to human urinary bladder carcinomas and B lymphocytes.

Full Citation AUTHORS: Paulie S, Ehlin-Henriksson B, Mellstedt H, Koho H, Ben-Aissa H, Perlmann P

SOURCE: Cancer Immunol Immunother. 1985;20(1):23-8.

Related Articles CIT. IDS: PMID: 2998589 UI: 86053082

☐ TITLE: Monoclonal antibodies to antigens associated with transitional cell carcinoma of the human urinary bladder. II. Identification of the cellular target structures by immunoprecipitation and SDS-PAGE analysis.

Full Citation AUTHORS: Paulie S, Koho H, Ben-Aissa H, Hansson Y, Lundblad ML, Perlmann P

SOURCE: Cancer Immunol Immunother. 1984;17(3):173-9.

Related Articles CIT. IDS: PMID: 6383601 UI: 85001868

Printed 10/03/

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET N
09/328,296	06/08/1999	800	1642	9632-005

APPLICANT
CLAY B SIEGALL, EDMONDS, WASHINGTON; ALAN F WAHL, MERCER ISLAND, WASHINGTON; JOSEPH A FRANCISCO, EDMONDS, WASHINGTON; HENRY JPERRY FELL, REDMOND, WASHINGTON.

CONTINUING DOMESTIC DATA********
VERIFIED

371 (NAT'L STAGE) DATA********
VERIFIED

FOREIGN APPLICATIONS********
VERIFIED

FOREIGN FILING LICENSE GRANTED 07/28/1999

SMALL ENTITY

Foreign priority claimed / 35 USC 119 (a-d) conditions met / Verified and acknowledged	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDE CLAIMS
O yes O no / O yes O no O Met after Allowance / Examiner's Name Initials	WA	10	37	26

ADDRESS
PENNIE & EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK , NY 10036-2711

TITLE
RECOMBINANT ANTI-CD40 ANTIBODY AND USES THEREOF

FILING FEE RECEIVED $*1686	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	O All Fees O 1.16 Fees (Filing) O 1.17 Fees (Processing Ext. of Tim O 1.18 Fees (Issue) O Other _____ O Credit

L15 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:121914 BIOSIS
DOCUMENT NUMBER: PREV199800121914
TITLE: IL-5 and IL-5 receptor in asthma.
AUTHOR(S): Kotsimbos, A. T. C.; Hamid, Q. (1)
CORPORATE SOURCE: (1) Dep. Med., Meakins-Christie Lab., McGill Univ., 3626 rue St. Urbain, Montreal, PQ H2X 2P2 Canada
SOURCE: Memorias do Instituto Oswaldo Cruz, (Dec. 30, 1997 (1998)) Vol. 92, No. SUPPL. 2, pp. 75-91.
ISSN: 0074-0276.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB Eosinophils, along with mast cells are key cells involved in the innate immune response against parasitic infection whereas the adaptive immune response is largely dependent on lymphocytes. in chronic parasitic disease and in chronic allergic disease, IL-5 is predominantly a T cell derived cytokine which is particularly important for the terminal differentiation, activation and survival of committed eosinophil precursors. The human IL-5 gene is located on chromosome 5 in a gene cluster that contains the evolutionary related IL-4 family of cytokine genes. The human IL-5 receptor complex is a heterodimer consisting of a unique a subunit (predominantly expressed on eosinophils) and a beta subunit which is shared between the receptors for IL-3 & GM-CSF (more widely expressed). The alpha subunit is required for ligand-specific binding whereas association with the beta subunit results in **increased binding** affinity. The alternative splicing of the alphaIL-5R gene which contains 14 exons can yield several alphaIL-5R isoforms including a membrane-anchored isoform (alphaIL-5Rm) and a soluble isoform (alphaIL-5Rs). Cytokines such as IL-5 produce specific and non-specific cellular responses through specific cell membrane receptor mediated activation of intracellular signal transduction pathways which, to a large part, regulate gene expression. The major intracellular signal transduction mechanism is activation of non-receptor associated tyrosine kinases including JAK and MAP kinases which can then transduce signals via a novel family of transcriptional factors named signal transducers and activators of transcription (STATS). JAK2, STAT1 and STAT5 appear to be particularly important in IL-5 mediated eosinophil responses. Asthma is characterized by episodic airways obstruction, increased bronchial responsiveness, and airway inflammation. Several studies have shown an association between the number of activated T cells and eosinophils in the airways and abnormalities in FEV1, airway reactivity and clinical severity in asthma. It has now been well documented that IL-5 is highly expressed in the bronchial mucosa of atopic and intrinsic asthmatics and that the increased IL-5 mPNA present in airway tissues is predominantly T cell derived. Immunocytochemical staining of bronchial biopsy sections has confirmed that IL5 mRNA transcripts are translated into protein in asthmatic subjects. Furthermore, the number of activated CD4+ T cells and IL-5 mRNA positive cells are increased in asthmatic airways following antigen challenge and studies that have examined IL-5 expression in asthmatic subjects before and after steroids have shown significantly decreased expression following oral corticosteroid treatment in

steroid-sensit[redacted] asthma but not in steroid res[redacted]ant and chronic severe steroid depende[redacted] asthma. The link between T ce[redacted]derived IL-5 and eosinophil activation in asthmatic airways is further strengthened by the demonstration that there is an increased number of alphaIL-5R mRNA positive cells in the bronchial biopsies of atopic and non-atopic asthmatic subjects and that the eosinophil is the predominant site of this increased alphaIL-5R mRNA expression. We have also shown that the subset of activated eosinophils that expressed mRNA for membrane bound alphaIL5r inversely correlated with FEV1, whereas the subset of activated eosinophils that expressed mRNA for soluble alphaIL5r directly correlated with FEV1. Hence, not only does this data suggest that the presence of eosinophils expressing alphaIL-5R mRNA contribute towards the pathogenesis of bronchial asthma, but also that the eosinophil phenotype with respect to alpha IL5R isoform expression is of central importance. Finally, there are several animal, and more recently in vitro lung explant, models of allergen induced eosinophilia, late airway responses (LARS), and bronchial hyperresponsiveness (BHR) - all of which support a link between IL-5 and airway eosinophila and bronchial hyperresponsiveness. The most direct demonstration of T cell involvement in LARS is the finding that these physiological responses can be transferred by CD4+ but not CD8+ T cells in rats. The importance of IL-5 in animal models of allergen induced bronchial hyperresponsiveness has been further demonstrated by a number of studies which have indicated that IL-5 administration is able to induce late phase responses and BHR and that anti-IL-5 antibody can block allergen induced late phase responses and BHR. In summary, activated T lymphocytes, IL5 production and eosinophil activation are particularly important in the asthmatic response. Human studies in asthma and studies in allergic animal models have clearly emphasized the unique role of IL-5 in linking T lymphocytes and adaptive immunity, the eosinophil effector cell, and the asthma phenotype. The central role of activated lymphocytes and eosinophils in asthma would argue for the likely therapeutic success of strategies to block T cell and eosinophil activation (e.g. steroids). Importantly, more targeted therapies may avoid the complications associated with steroids. Such therapies could target key T cell activation proteins and cytokines by various means including blocking antibodies (e.g. anti-CD4, **anti-CD40**, **anti** -IL-5 etc), antisense oligonucleotides to their specific mRNAs, and/or selective inhibition of the promoter sites.for these genes. Another option would be to target key eosinophil activation mechanisms including the alphaIL5r. As always, the risk to benefit ratio of such strategies await the results of well conducted clinical trials.

L15 ANSWER 2 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 96305412 MEDLINE
DOCUMENT NUMBER: 96305412
TITLE: CD40-mediated regulation of interleukin-4 signaling pathways in B lymphocytes.
AUTHOR: Siepmann K; Wohlleben G; Gray D
CORPORATE SOURCE: Department of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital, London, GB.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1996 Jul) 26 (7) 1544-52. Journal code: EN5. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199611
AB The importance of cytokines in controlling immunoglobulin isotype switching is well known. Given the defect in switching to IgG, IgA and IgE

isotypes in mi[redacted] and humans that carry mutation[redacted]n the CD40 and CD40 ligand genes, [redacted] have investigated the role of [redacted]40 ligation in controlling B cell responses to interleukin (IL)-4. We have found that CD40-mediated signals cause a fivefold upregulation of IL-4 receptor (IL-4R) on the B cell surface and that this is associated with a 100-1000-fold increase in the cells' responsiveness to the cytokine. While we found no evidence of **increased affinity** or structural change of the receptor, we do find that prestimulation of B cells with **anti-CD40 antibodies** brings about several changes in the IL-4 signaling pathways. Subsequent delivery of IL-4 to CD40-prestimulated cells provokes intracellular signals distinct from those induced in resting B cells in response to IL-4. While resting B cells phosphorylate Jak3 kinase shortly after IL-4 activation, cells pre-incubated with **anti-CD40** exhibit active dephosphorylation of this molecule and phosphorylation of proteins of around 45 kDa upon addition of IL-4. The common gamma chain, Jak3 and Jak1 can all be immunoprecipitated in normal amounts with the IL-4R chain after CD40 prestimulation. We show that the observed dephosphorylation of Jak3 may be due to a stable association with the src-homology protein tyrosine phosphatase SH-PTP2. In contrast, the enzyme appears to be inactive and to dissociate very quickly from the signaling complex in cells that are stimulated with IL-4 alone.

L15 ANSWER 3 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 96182279 MEDLINE
DOCUMENT NUMBER: 96182279
TITLE: The differentiation of human memory B cells into specific **antibody**-secreting cells is **CD40** independent.
AUTHOR: Silvy A; Lagresle C; Bella C; Defrance T
CORPORATE SOURCE: INSERM U 404, "Immunite et Vaccination" Institut Pasteur de Lyon, France.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1996 Mar) 26 (3) 517-24.

Journal code: EN5. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199607

AB It is generally accepted that memory B cells can be defined by their ability to produce, upon antigenic challenge, somatically mutated antibody molecules characterized by an **increased affinity** and by the expression of a downstream heavy chain isotype. However, the inability to isolate this particular B cell compartment has precluded the study of memory B lymphocyte physiology in man. We previously reported on the identification of an IgD- B cell subset in human tonsils that we defined as CD38- B cells, whose phenotype is highly reminiscent of that of memory B lymphocytes from the splenic marginal zone of rodents. In the present study, we developed a model of the measles virus (MV)-specific secondary antibody response in vitro to assess the presence of memory B lymphocytes in different B cell subsets isolated from human tonsils and explore the activation requirements of human memory B cells. Our findings show that the memory B cell pool resides in the CD38- B cell subpopulation and that the differentiation of MV-activated memory B cells into antibody-secreting cells can be achieved upon co-stimulation with

interleukin (I[redacted]2 and IL-10, but does not requ[redacted] engagement of CD40. Interestingly, [redacted]e CD40-mediated signal was fou[redacted] to synergize with Ig-cross-linking agents for the proliferation of memory B cells, but strongly suppressed their capacity to differentiate along the plasmacytoid pathway. Collectively, our results suggest that the CD40 signaling pathway is instrumental for the clonal expansion of the memory B cell pool, but does not operate in the later phase of the response, which allows their maturation into antibody-secreting cells.

L15 ANSWER 4 OF 4 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 95036341 MEDLINE
DOCUMENT NUMBER: 95036341
TITLE: **Anti-CD40 antibody** binding modulates human multiple myeloma clonogenicity in vitro.
AUTHOR: Tong A W; Zhang B Q; Mues G; Solano M; Hanson T; Stone M J
CORPORATE SOURCE: Cancer Immunology Research Laboratory, Charles A. Sammons Cancer Center, Baylor University Medical Center, Dallas, TX 75246.
SOURCE: BLOOD, (1994 Nov 1) 84 (9) 3026-33.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199502

AB Ligand binding of the B-cell lineage antigen CD40 enhances growth and interleukin-6 (IL-6) secretion in human B cells (the CD40/IL-6 loop). IL-6 has an autocrine and paracrine role in human multiple myeloma (MM) cell growth. With the use of the **CD40** monoclonal **antibody** (MoAb) G28-5, we examined CD40 expression and the effect of CD40 binding on MM clonogenic colony (MCC) formation to characterize the IL-6/CD40 loop activity in MM. CD40 was expressed on plasmacytoid cells in 21 of 28 plasma cell dyscrasia (PCD) bone marrow (BM) biopsies tested (10 of 14 MM, 2 of 2 Waldenstrom's macroglobulinemia [WM], 2 of 2 plasma cell leukemia [PCL], 6 of 8 monoclonal gammopathy of undetermined significance [MGUS], and 1 of 2 primary amyloidosis [AL]). G28-5 **binding increased** MCCs by 35% to 150% in 11 of 17 CD40+ PCD BM cultures, but did not affect MCC formation in CD40- specimens or normal BM colony forming units (CFU-GEMM, CFU-GM, BFU-E). Responsive cultures originated from BM of patients with MM (2 of 5 cases tested), WM (2 of 2), PCL (2 of 2), and MGUS (5 of 6). CD40-responsiveness was not significantly inhibited by the presence of an anti-IL-6 MoAb (2 of 2 MGUS cultures tested), and did not correlate with the capacity to respond to IL-6 stimulation ($n = 17$, $P > .05$) or a detectable level of endogenous IL-6 ($n = 15$, $P > .05$). Additional studies were performed with PCD cell lines to characterize the interrelationship of CD40 activation and IL-6 production. Fifty percent to greater than 95% of cells from the RPMI 8226 and ARH77 lines expressed CD40, whereas 6% of U266 cells were CD40+. For RPMI 8226, ARH-77, and U266 cells, the increased MCC formation after **anti-CD40** stimulation was not affected by the presence of an anti-IL-6 neutralizing MoAb and was not accompanied by detectable IL-6 secretion. There was no apparent increase in IL-6 mRNA transcription following G28-5 treatment of U266 or RPMI 8226 cells. Our observations indicate that CD40 is expressed in a subset of human myeloma cells present in various PCDs. Cell-line studies suggest that the CD40+ myeloma cell may regulate MM clonogenic

colony formati[redacted] without activating the IL-6 pa[redacted]ay.

L3 ANSWER 1 OF 9 MEDLINE
ACCESSION NUMBER: 96245984 MEDLINE
DOCUMENT NUMBER: 96245984
TITLE: CD40 antibodies defining distinct epitopes display qualitative differences in their induction of B-cell differentiation.
AUTHOR: Bjorck P; Paulie S
CORPORATE SOURCE: Department of Immunology, Stockholm University, Sweden.
SOURCE: IMMUNOLOGY, **(1996 Feb)** 87 (2) 291-5.
Journal code: GH7. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199611

AB IgE production can be obtained in vitro by stimulating B lymphocytes with CD40 antibodies and interleukin-4 (IL-4). This stimulation also results in homotypic aggregation and cell proliferation. We have shown previously that IgE synthesis may be dependent on additional signals provided by the close cellular contact. Thus inhibition of the aggregation by lymphocyte function-associated antigen-1 (LFA-1) antibodies leads to a decrease in IgE production. In the present study we show that the inhibitory effect of LFA-1 antibodies is critically dependent on the CD40 antibody used for stimulation. Thus, while previously using the monoclonal antibody (mAb) **S2C6**, IgE production induced by the CD40 antibody mAb89 was generally higher and could be enhanced more than fivefold in the presence of LFA-1 antibodies. Similarly, the addition of the CD23 mAb MHM6, which blocked aggregation to a similar degree as the LFA-1 antibodies, inhibited **S2C6**-induced IgE production but enhanced that induced by mAb89. In contrast to these opposing effects on IgE synthesis, proliferation induced by the two CD40 antibodies was affected similarly by the blocking antibodies. As the interaction between CD23 and CD21 has been suggested to involve recognition of carbohydrate structures on CD21 by the lectin-like domain on CD23, we also tested the effect of some different sugars on IgE synthesis and proliferation. Addition of fucose-1-phosphate to anti-CD40 and IL-4-stimulated B cells completely inhibited IgE synthesis and proliferation. Inhibition was also seen with mannose-6-phosphate but not with glucose-1-phosphate. In contrast to the MHM6 antibody, the effect of the sugars was similar irrespective of the CD40 antibody used for stimulation. The study shows that different antibodies to CD40 may give rise to qualitatively distinct signals depending on the epitope recognized.

L3 ANSWER 2 OF 9 MEDLINE
ACCESSION NUMBER: 95137673 MEDLINE
DOCUMENT NUMBER: 95137673
TITLE: Antibodies to distinct epitopes on the CD40 molecule co-operate in stimulation and can be used for the detection of soluble CD40.
AUTHOR: Bjorck P; Braesch-Andersen S; Paulie S
CORPORATE SOURCE: Department of Immunology, Stockholm University, Sweden..
SOURCE: IMMUNOLOGY, **(1994 Nov)** 83 (3) 430-7.

Journal code: GH7. ISSN: 0019-28
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199505

AB The B-cell surface protein, CD40, belongs to the tumour necrosis factor/nerve growth factor (TNF/NGF) receptor family and plays a crucial role in T cell-dependent B-cell activation. Ligation of this receptor with antibodies or its recently defined ligand, gp39, generates an intracellular signal that, when combined with triggering of surface immunoglobulin or the interleukin-4 (IL-4) receptor, induces a variety of stimulatory effects in B cells. In this study we provide further evidence for the importance of receptor cross-linking in generating this signal and we also report on the presence of a soluble form of CD40. A new CD40 monoclonal antibody (mAb), 17:40, was found to synergize with other CD40 antibodies (mAb89 and **S2C6**) in inducing proliferation as well as IgE synthesis in IL-4-treated tonsillar B cells. However, both this mAb and mAb89 failed to co-operate with a soluble construct of the CD40 ligand, whereas such co-operation was seen with the **S2C6** antibody. Cross-inhibition experiments showed that the 17:40 mAb recognized an epitope that was clearly distinct from that seen by **S2C6** and mAb89. Although directed to separate epitopes, both 17:40 and mAb89 completely blocked binding of gp39 to its receptor, while the **S2C6** mAb only partially interfered with this binding. The findings suggest a close relationship between the degree of receptor clustering and the strength of the delivered signal. With the access to antibodies recognizing distinct structures on CD40 we also established a sandwich enzyme-linked immunosorbent assay for quantitative determinations of the antigen. With this assay we could demonstrate the presence of a soluble form of CD40 (sCD40) in culture supernatants. The fact that sCD40 also retained its ligand-binding capacity indicates that it may have an important regulatory role and modulate the T cell-dependent stimulation via CD40. Both the finding of soluble receptors and the need for receptor clustering are features that CD40 share with other members of the TNF/NGF receptor family.

L3 ANSWER 3 OF 9 MEDLINE
ACCESSION NUMBER: 94011036 MEDLINE
DOCUMENT NUMBER: 94011036
TITLE: CD40 plays an essential role in the activation of human B cells by murine EL4B5 cells.
AUTHOR: Kwekkeboom J; De Boer M; Tager J M; De Groot C
CORPORATE SOURCE: Laboratory of Cell Biology and Histology, University of Amsterdam, Academic Medical Center, The Netherlands.
SOURCE: IMMUNOLOGY, **(1993 Jul)** 79 (3) 439-44.
Journal code: GH7. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199401

AB A mutant subclone of the murine thymoma EL-4, known as EL4B5, can strongly activate human B cells to proliferate and differentiate in a cell-cell contact-dependent manner. We have investigated whether interaction via CD40 plays a role in this helper activity. For this purpose, three newly generated anti-CD40 monoclonal antibodies (mAb) were used. In contrast with other anti-CD40 mAb described in the literature, these mAb did not co-stimulate proliferation of human B cells. On the other hand, these novel mAb could inhibit the co-stimulatory effect of the previously described anti-CD40 mAb **S2C6** on anti-IgM-induced human B-cell

proliferation. It was found that addition of the non-stimulatory anti-CD40 mAb could completely inhibit EL4B5-induced human B-cell proliferation. Maximal inhibition occurred already at a mAb concentration of 10 ng/ml. Similarly, a fusion protein, consisting of the extracellular portion of CD40 and human IgM constant domains CH2, CH3 and CH4, could completely inhibit EL4B5-induced human B-cell proliferation. Induction of human B-cell proliferation by EL4B5 cells was also inhibited by anti-CD40 mAb **S2C6** and G28.5, but less effectively. In contrast, mAb against B-cell surface antigens CD20 or B7 had no inhibitory effects. It is concluded that interaction via CD40 is essential for the induction of human B-cell proliferation by EL4B5 cells.

L3 ANSWER 4 OF 9 MEDLINE
ACCESSION NUMBER: 92348908 MEDLINE
DOCUMENT NUMBER: 92348908
TITLE: Agonistic properties of anti-B cell antibodies purified on staphylococcal protein A may be due to contaminating protein A.
AUTHOR: Jakobson E; Axelsson B; Paulie S
CORPORATE SOURCE: Department of Immunology, Stockholm University, Sweden..
SOURCE: JOURNAL OF IMMUNOLOGICAL METHODS, **(1992 Jul 31)** 152 (1) 49-57.
Journal code: IFE. ISSN: 0022-1759.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199211

AB Some antibodies directed to cell surface receptors may mimic the physiological ligands by inducing the transmission of activation or growth signals. Such agonistic antibodies have proven very useful when studying functional properties of various receptor molecules on, e.g., lymphoid cells. However, while investigating the agonistic effects on tonsillar B cells of the anti-CD43 monoclonal antibody (mAb) D4B11 and the anti-CD40 mAb **S2C6**, we made some observations which emphasize the need for caution when using antibodies purified by protein A affinity chromatography. Both antibody preparations were found to elicit changes in the intracellular free calcium concentration ([Ca2+]i) as well as promoting proliferation of phorbol ester activated cells. However, a closer analysis showed that the increase in [Ca2+]i could be attributed to soluble staphylococcal protein A (SpA) desorbed during antibody purification. By using pure soluble SpA, we were able to show that nanogram amounts were sufficient to increase [Ca2+]i by a mechanism that involved both a mobilization from intracellular stores and an influx across the B cell membrane. A similar effect on cytosolic Ca2+ in B cells was also noted for streptococcal protein G (protein G), another bacterial component used for antibody purification. However, in contrast to SpA, protein G had little effect on cell proliferation. These observations suggest that the presence of trace amounts of SpA or protein G in antibodies purified on these bacterial components may lead to incorrect interpretations of the agonistic properties of such antibodies. When the above findings were taken into account, it was found that the CD43 mAb D4B11, like the CD40 mAb **S2C6**, stimulated growth of B cells without causing any measurable increase in [Ca2+]i. Both CD40 and CD43 may thus be coupled to signalling pathways which do not involve breakdown of membrane phosphoinositides.

L3 ANSWER 5 OF 9 MEDLINE
ACCESSION NUMBER: 89093945 MEDLINE
DOCUMENT NUMBER: 89093945
TITLE: The human B lymphocyte and carcinoma antigen, CDw40, is a

AUTHOR: [redacted]osphoprotein involved in growt[redacted]ignal transduction.
aulie S; Rosen A; Ehlin-Henriks[redacted]n B; Braesch-Andersen S; Jakobson E; Koho H; Perlmann P

CORPORATE SOURCE: Department of Immunology, University of Stockholm, Sweden.

SOURCE: JOURNAL OF IMMUNOLOGY, **(1989 Jan 15)** 142 (2) 590-5.
Journal code: IFB. ISSN: 0022-1767.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals

ENTRY MONTH: 198904

AB The human B lymphocyte and carcinoma-associated Ag, CDw40, (p50, Bp50) is a receptor candidate for normal growth regulation. Interaction of mAb with this pan-B Ag, together with preactivating agents such as 12-O-tetradecanoylphorbol-13-acetate or anti-mu, deliver strong growth-promoting signals to the cells. We here demonstrate that signaling through this Ag is dependent on its aggregation on the cell surface. Thus, monovalent antibody fragments were relatively inefficient in this respect but effectively blocked stimulation by intact antibody. By using affinity purified CDw40 protein we have also demonstrated that it is antigenically distinct from other B cell-associated Ag, including the six differentiation clusters CD19 to CD24. The mAb **S2C6** and G28.5, prepared by immunizing mice with human bladder carcinoma cells or tonsillar B-cells, respectively, were the only antibodies giving detectable binding. Either of these antibodies could also completely block the binding of the other, suggesting an identity or structural proximity of the epitopes recognized. The CDw40 Ag was shown to be a phosphoprotein lacking intrinsic protein kinase activity. The results provide further evidence for CDw40 being an important B cell growth factor receptor which may also have growth regulatory functions in the development of certain human carcinomas.

L3 ANSWER 6 OF 9 MEDLINE

ACCESSION NUMBER: 87059074 MEDLINE

DOCUMENT NUMBER: 87059074

TITLE: Isolation and characterization of two bladder carcinoma-associated antigens.

AUTHOR: Braesch-Andersen S; Paulie S; Koho H; Perlmann P

SOURCE: JOURNAL OF IMMUNOLOGICAL METHODS, **(1986 Nov 20)** 94 (1-2) 145-51.
Journal code: IFE. ISSN: 0022-1759.

PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 198703

AB By the use of mouse monoclonal antibodies we have earlier defined five distinct antigens associated with transitional cell carcinoma of the human urinary bladder (TCC). Two of these antigens have now been purified and partially characterized. For their purification from isolated tumor cell membranes, a rapid and efficient method of affinity chromatography was developed in which the coupling of monoclonal antibodies to protein A-Sepharose was fortified by treatment with glutaraldehyde. From these columns, 60-80% of the antigenic activity present in membrane lysates could be recovered by acid elution, corresponding to approximately 0.25-0.5 micrograms antigen protein per mg membrane protein added. The two isolated antigens are relatively hydrophobic membrane components not found

in normal bladder tissue. The antigen defined by the monoclonal antibody **S2C6** is confined to bladder carcinoma and B cells. It is a glycosylated, ConA-binding polypeptide with Mr 50 000 as established by SDS-PAGE. It is acidic with an IP of 3.2, heat stable up to 85 degrees C, stable at low pH (2.0) but sensitive to SDS. The antigen defined by the monoclonal antibody 7E9 is confined to bladder carcinoma but is also weakly expressed in some blood vessel endothelium. It consists of two main polypeptides of Mr 29,000 and 23,000 which do not bind to ConA. It has an IP of 7.4 and its antigenic activity is abolished by heating to 50 degrees C for 5 min. As the **S2C6** antigen, it is stable at low pH but susceptible to SDS.

L3 ANSWER 7 OF 9 MEDLINE
ACCESSION NUMBER: 86053082 MEDLINE
DOCUMENT NUMBER: 86053082
TITLE: A p50 surface antigen restricted to human urinary bladder carcinomas and B lymphocytes.
AUTHOR: Paulie S; Ehlin-Henriksson B; Mellstedt H; Koho H; Ben-Aissa H; Perlmann P
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, **(1985)** 20 (1) 23-8.
Journal code: CN3. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198603

AB We have previously described the derivation of a monoclonal antibody, **S2C6**, to a novel 50 Kdalton antigen associated with human urinary bladder carcinoma. No reactions were obtained with carcinomas of unrelated origin or with normal urothelial cells. However, the antibody also reacted with a similar antigen on some cell lines of B lymphocyte origin. Using large panels of target cells we have now shown that this reactivity was entirely restricted to cells of the B lineage within the haematopoietic system. As opposed to its apparent restriction to malignant cells of the urothelium, the **S2C6** antigen was expressed by normal B lymphocytes as well as by many malignant B cells (chronic lymphocytic leukaemia, hairy cell leukaemia and immunocytoma). Pre-B cells derived from acute lymphocytic leukaemia and plasma cells from multiple myeloma lacked the antigen. Expression was significantly enhanced on cultured B cells from Burkitt lymphomas and on Epstein-Barr virus-transformed lymphoblastoid cell lines including those of the pre-B phenotype derived from fetal bone marrow. As judged from the molecular size and the distribution pattern displayed by the **S2C6** antigen it appears to be distinct from other B cell antigens previously described. A possible relation of the **S2C6** antigen to a receptor for B cell growth factors is discussed.

L3 ANSWER 8 OF 9 MEDLINE
ACCESSION NUMBER: 85257727 MEDLINE
DOCUMENT NUMBER: 85257727
TITLE: Monoclonal antibodies against human urinary bladder carcinomas: selectivity and utilization for gamma scintigraphy.
AUTHOR: Bubenik J; Kieler J; Perlmann P; Paulie S; Koho H; Christensen B; Dienstbier Z; Koprivova H; Pospisil J; Pouckova P; et al
SOURCE: EUROPEAN JOURNAL OF CANCER AND CLINICAL ONCOLOGY, **(1985 Jun)** 21 (6) 701-10.
Journal code: ENW. ISSN: 0277-5379.
PUB. COUNTRY: ENGLAND: United Kingdom

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198511

AB Mouse monoclonal antibodies to human urinary bladder carcinoma cells have been examined by indirect membrane immunofluorescence using a panel of 27 human cell lines. Two of the monoclonal antibodies, 7E9 (IgG3) and **S2C6** (IgG1), were found to distinguish between urinary bladder carcinoma cells and normal urothelium. The third monoclonal antibody, T24.06.5(IgG1), discriminated among cell lines of urothelial and non-urothelial origin but did not distinguish between urinary bladder carcinoma and normal urothelial cells. None of the of the antibodies was found to be strictly selective, and occasional cross-reactions with unrelated cell types were observed. The monoclonal antibody 7E9, showing the highest degree of selectivity, was further examined by an indirect immunoperoxidase technique on frozen tissue sections from 19 patients. The antibody reacted with all (7/7) bladder carcinomas examined and gave negative results with control normal bladder mucosa (0/8) and unrelated tumor tissue (0/4) sections. The 7E9 antibody was purified by protein A affinity chromatography, labeled with 131I and used for gamma-scintigraphy in nude mice xenografted with human urinary bladder carcinoma T24. The 7E9 antibody was capable of locating the T24 xenografts in nude mice; it localized preferentially in the T24 tissue compared to normal mouse tissues. The T24 xenografts could not be detected by gamma-scintigraphy with 131I-labeled monoclonal antibody against human mammary carcinoma cells and two other control antibodies. Likewise the 131I-labeled 7E9 antibody was not capable of locating human mammary carcinoma xenografts in nude mice.

L3 ANSWER 9 OF 9 MEDLINE
ACCESSION NUMBER: 85001868 MEDLINE
DOCUMENT NUMBER: 85001868
TITLE: Monoclonal antibodies to antigens associated with transitional cell carcinoma of the human urinary bladder. II. Identification of the cellular target structures by immunoprecipitation and SDS-PAGE analysis.
AUTHOR: Paulie S; Koho H; Ben-Aissa H; Hansson Y; Lundblad M L; Perlmann P
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, **(1984)** 17 (3) 173-9.
Journal code: CN3. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: English
ENTRY MONTH: Priority Journals; Cancer Journals
198501

AB The cellular target structures for six monoclonal antibodies raised against cultured human bladder carcinoma cells (TCC) were investigated. The specificities of these antibodies when tested against a large panel of cells have been described in the companion paper. Radiolabeled cell lysates were precipitated with the different monoclonal antibodies bound to protein A (Staphylococcus aureus) on a matrix of Sepharose beads. The precipitates were separated by sodium dodecyl sulfate- gel electrophoresis (SDS-PAGE) and analyzed by autoradiography. The antibodies 4B5, 7E9, and 14B11 have previously been found to react in a similar way with TCC-targets and some non-TCC tumor cells, but not with normal urothelial cells or cells of hematopoietic origin. When tested with lysates of a TCC-cell line (TCCSuP) a strong 92K band and a weak 23K band were precipitated with any one of these antibodies. These polypeptides were

expressed on the cell surface and were not linked by disulfide bonds. Depletion experiments confirmed that the three antibodies recognized the same antigens. Another antibody (4E8) probably directed to a differentiation antigen present on both urothelial and melanoma cells detected two high molecular polypeptides, 190K and 170K. Antibodies from the **S2C6** hybridoma, which displayed a distinct dual specificity for TCC- targets and for malignant or transformed cells of B cell origin, precipitated a 50K component from extracts of either TCC- or B cell-derived cell lines. Antibodies produced by the S2A9 hybridoma were shown to bind to a framework epitope of the HLA-A, B, C heavy chain.